Combinatorial Chemistry - An Online Journal 16 (2014) 45–47

Contents lists available at ScienceDirect

Combinatorial Chemistry - An Online Journal

journal homepage: www.elsevier.com/locate/comche

Combinatorial Chemistry Online Volume 16, Issue 12, December 2014

N.K. Terrett

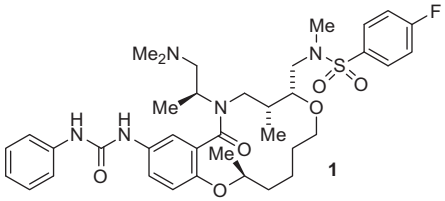
Ensemble Therapeutics Corp., Cambridge, MA 02139, USA

Current literature highlights

Diversity-oriented synthesis and the development of novel antimalarials

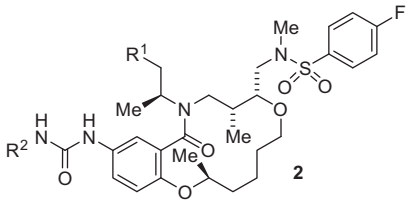
Malaria is widely recognised as a major threat to human health, but despite the urgency in finding novel antimalarial compounds, no new class of agent has been introduced into clinical use since 1996. The need becomes even more acute when the recent emergence of drug-resistant strains is considered. A recent paper describes the diversity-oriented synthesis of macrocyclic antimalarial agents, and demonstrates how comprehensive structural modification resulted in a compound with improved physical properties [1].

In a previous study a library approach to making macrocycles involved building diverse building blocks, coupling these into linear precursors and a final pairing of functionality to produce cyclic products – a so-called build/couple/pair approach. Macrocycles prepared using this strategy were found to have antimalarial properties, and compound **1** in particular has potent activity against both wild type 3D7 and multidrug resistant D2d strains of *Plasmodium falciparum*. However, analysis of this compound revealed a potential hERG liability and poor mouse microsome stability as well as poor solubility, making it unsuitable for further development. This recent study further investigated this series of macrocycles with the intention of improving these physical properties.



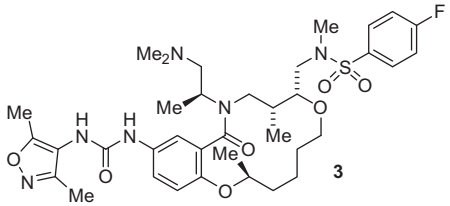
1

The macrocycle contains three positions that can readily be diversified – the exocyclic dimethylamino group (R1), the aniline-based urea (R2), and the exocyclic sulphonamide (**2**). The approach focused on the first two of these, as it had been previously demonstrated that the sulphonamide was essential for antimalarial activity. In addition, the build/couple/pair strategy was employed to investigate the contributions made by the rest of the molecule and thus identify the minimum pharmacophore required for activity.



2

Ultimately through these structural changes it was possible to develop the structure–activity relationships of this series, and simultaneously profile compounds for hERG activity and physical properties. Ultimately, compound **3** was selected for *in vivo* profiling in a *Plasmodium berghei* malaria mouse model. The goal was to find a compound that has exposure *in vivo* exceeding three times the GI_{50} concentration. Intraperitoneal administration of compound **3** at 20 mg/kg demonstrated that sufficient exposure could be achieved for around 5 h. Administering the compound seven times at 100 mg/kg every 12 h over 3 days in the *P. berghei* malaria mouse model produced a twofold reduction in total parasitemia. Although a significant reduction, this is not quite at the levels seen with standard of care antimalarial compounds and thus more compound development is still required.



3

Overall, this study was successful in using diversity-oriented synthesis to explore SAR and physical properties, and in finding a potent antimalarial compound with some level of exposure and efficacy in a malarial mouse model.

A summary of the papers in this month's issue

Polymer supported synthesis

A facile and expedient route to the synthesis of arylopeptoid oligomers (*N*-alkylated aminomethyl benzamides) using a semi-automated microwave-assisted solid-phase synthesis has been

E-mail: nterrett@ensembletx.com

http://dx.doi.org/10.1016/j.comche.2014.11.001

described. The synthesis was optimised for the incorporation of side chains derived from sterically hindered or unreactive amines and both *ortho*- and *para*-substituted arylo-backbones. By using this optimised protocol, a complex nonameric arylopeptoid, featuring a novel alternating *ortho*-, *meta*-, and *para*-substituted backbone pattern and a variety of chemically diverse and challenging side chains has been synthesised in less than 11 h [2].

A one-bead-two-compound (OBTC) library of structurally rigidified bicyclic peptides has been chemically synthesised on TentaGel microbeads (90 μm), with each bead displaying a unique bicyclic peptide on its surface and a linear encoding peptide of the same sequence in its interior. Screening of the library against oncogenic K-Ras G12V mutant identified two classes of Ras ligands. Class I ligands apparently bind to the effector-binding site and inhibit the Ras–Raf interaction, whereas class II ligands appear to bind to a yet unidentified site different from the effector-binding site. These Ras ligands provide useful research tools and may be further developed into therapeutic agents [3].

Nobilamide B is a long-acting antagonist of transient receptor potential vanilloid-1, and is expected to show therapeutic potential for treatment of pain. This linear heptapeptide possesses a *Z*-didehydroaminobutanoic acid moiety at the *C*-terminus that could be stereoselectively constructed by application of the traceless Staudinger ligation. Combining solid-phase peptide synthesis and the Staudinger ligation allowed rapid access to not only nobilamide B, but also its macrocyclic analogue nobilamide D [4].

Solution-phase synthesis

A simple, convenient and efficient protocol for the construction of an array of glycospiro-pyrroloisoquinolines using isoquinolinium ylide and a carbohydrate-derived exocyclic olefin in the presence of a $Cu(OTf)_2$–Et_3N catalytic system has been described. Isoquinoline and alkylbromoacetates/2-bromoacetophenones were employed to generate the azomethine ylides in the presence of Et_3N in refluxing toluene, and subsequent exposure to the olefin led to the desired isoquinoline derivatives [5].

Scaffolds and synthons for combinatorial libraries

No papers this month.

Solid-phase supported reagents

A simple and efficient synthetic protocol for the synthesis of 5-substituted 1*H*-tetrazole derivatives through the [2+3] cycloaddition of nitriles with sodium azide using ceric ammonium nitrate supported HY-zeolite as a novel catalyst has been reported. Excellent yields of the corresponding tetrazoles were obtained through this cost-effective protocol under mild aerobic reaction conditions with short reaction times [6].

An efficient and ecofriendly aldol reaction of kojic acid with aldehydes using a heterogeneous reusable catalyst (alumina modified with base) has been developed. Enzymatic hydrolytic resolution of a racemic acetylated aldol adduct was achieved using lipase from *Candida Antarctica* type B. The key feature of this enzymatic resolution is that regioselective deacetylation of the ester, derived from a primary alcohol located away from the stereocentre, occurred in the presence of an adjacent secondary acetate [7].

Novel resins, linkers and techniques

An alkoxyamine linker has been applied for the solid-phase synthesis of benzazoles, quinazolines, and quinazolinones. Aromatic aldehydes were anchored by aldoxime linkage, and after reaction on a solid support, the products were cleaved with paraformaldehyde under acidic conditions to afford the corresponding aldehydes. These were subsequently subjected to oxidative coupling with 2-substituted anilines under air atmosphere to give the desired compounds [8].

Library applications

Phenyl imidazolidin-2-one has been introduced as a linker for novel HDAC inhibitors. A focused library of 20 compounds were designed and synthesised, from which eight compounds showed equivalent or higher potencies against HDAC1 than vorinostat. *In vitro* antitumor activity assays in HCT-116, PC-3 and HL-60 cancer cells revealed six compounds with potent antitumor activities. In an HCT-116 nude mice xenograft model, one compound displayed significant antitumour activity in both continuous and intermittent dosing schedules [9].

A small library of benzimidazole functionalised chiral thioureas has been prepared starting from natural amino acids (*S*)-alanine, (*S*)-phenylalanine, (*S*)-valine and (*S*)-leucine and also their (*R*)-isomers Their antimicrobial activity against various Gram-positive and Gram-negative bacterial strains such as *Staphylococcus aureus*, *Bacillus subtilis*, *Micrococcus luteus*, *Klebsiella planticola*, *Escherichia coli* and *Pseudomonas aeruginosa* have been investigated. In a cytotoxicity study, thioureas derived from non-natural amino acids showed good activity against human cancer cell lines A549, MCF7, DU145, and HeLa [10].

Histidinol dehydrogenase (HDH) has been established as a virulence factor for the human pathogen bacterium *Brucella suis*. Targeting such a virulence factor is a relevant anti-infectious approach as it could decrease the frequency of antibiotic resistance. The synthesis of a library of oxo- and thioxo-imidazo[1,5-*c*]pyrimidines, potential enzyme inhibitors of HDH, has been described in a recent paper [11].

A water-mediated protocol for the efficient synthesis of a library of 2-amino-6-styryl pyrimidines and their dihydro analogues has been reported. Most of the saturated compounds rather than their unsaturated analogues showed anti-bacterial (*in vitro*) activity against three human pathogens viz. *S. aureus*, *Klebsiella pneumonia* and *E. coli* [12].

Aminoglycoside-2″-O-nucleotidyltransferase ANT(2″)-Ia is an aminoglycoside resistance enzyme prevalent among Gram-negative bacteria, and is one of the most common determinants of enzyme-dependant aminoglycoside-resistance. A recent paper outlines the use of a recently described oxidopyrylium cycloaddition/ring-opening strategy in the synthesis and profiling of a library of synthetic α-hydroxytropolones against ANT(2″)-Ia. Two of these synthetic constructs are capable of rescuing gentamicin activity against ANT-(2″)-Ia-expressing bacteria [13].

On-going SAR efforts based on ML297, a potent, efficacious and selective GIRK1/2 activator (~10-fold *vs* GIRK1/4 and inactive on GIRK2/3), being investigated via an iterative parallel synthesis approach have been reported. The chemical optimisation at the 3-position of the pyrazole within ML297 indicated that various functionalised 3-cyclopropyl moieties modulated GIRK pharmacology between inhibitor/activator within a series of 1-(3-cyclopropyl-1-phenyl-1*H*-pyrazol-5-yl)ureas. Importantly, novel 'molecular switches' that modulated the mode of pharmacology from inhibitor to activator have been discovered on both the 3-cyclopropyl and *N*-phenyl moiety of the pyrazole core, providing the first highly selective GIRK1/2 activator [14].

The presence of a structural recognition motif for the nucleoside P2 transporter in a library of pyrimidine and triazine non-nucleoside HIV-1 reverse transcriptase inhibitors, has prompted the evaluation of antitrypanosomal activity. It has been demonstrated that the structure–activity relationship for anti-HIV and antitrypanosomal activity was not identical. Optimisation in the diaryl triazine

series led to 6-(mesityloxy)-N_2-phenyl-1,3,5-triazine-2,4-diamine, a compound with potent *in vitro* and moderate *in vivo* antitrypanosomal activity [15].

A polymer-supported route for the synthesis of sphingosine derivatives based on the *C*-acylation of polymeric phosphoranylidene acetates with an Fmoc-protected amino acid has been presented. The approach enables the flexible variation of the sphingosine tail through a deprotection–decarboxylation sequence followed by *E*-selective Wittig olefination cleavage. The effect of ceramides and keto-ceramides on the proliferation of three cancer cell lines HEP G-2, PC-12 and HL-60 was investigated and a ceramide containing an aromatic sphingosine tail was identified as being most active [16].

In order to develop affinity-based biosensor platforms, appropriate ligands with a functional handle for immobilisation onto a biosensor surface are required. To this end, a library of papain inhibitors has been designed and synthesised, containing different azide linkers for subsequent immobilisation by 'click' chemistry. Furthermore, a molecular docking study was performed to obtain a better insight as to at which position such azide handles could be tolerated without affecting binding affinity [17].

References

[1] Comer E, Beaudoin JA, Kato N, Fitzgerald ME, Heidebrecht RW, Lee MD, et al. Diversity-oriented synthesis-facilitated medicinal chemistry: toward the development of novel antimalarial agents. J Med Chem 2014;57(20):8496–502.

[2] Rasmussen JE, Boccia MM, Nielsen J, Taillefumier C, Faure S, Hjelmgaard T. Rapid and convenient semi-automated microwave-assisted solidphase synthesis of arylopeptoids. Tetrahedron Lett 2014;55(43):5940–3.

[3] Upadhyaya P, Qian Z, Habir NAA, Pei D. Direct Ras inhibitors identified from a structurally rigidified bicyclic peptide library. Tetrahedron 2014;70(42):7714–20.

[4] Yamashita T, Matoba H, Kuranaga T, Inoue M. Total syntheses of nobilamides B and D: application of traceless Staudinger ligation. Tetrahedron 2014;70(42):7746–52.

[5] Barman PD, Sanyal I, Mandal SB, Banerjee AK. Cu(OTf)2-promoted efficient synthetic route towards glycospiro-pyrrolo[2,1-a]isoquinolines. Tetrahedron Lett 2014;55(41):5648–51.

[6] Sivaguru P, Bhuvaneswari K, Ramkumar R, Lalitha A. Synthesis of 5-substituted 1H-tetrazoles catalyzed by ceric ammonium nitrate supported HY-zeolite. Tetrahedron Lett 2014;55(41):5683–6.

[7] Sharma DK, Singh B, Mukherjee D. Aldol reaction of kojic acid using alumina supported base catalyst and enzymatic resolution of the aldol adduct by CALB. Tetrahedron Lett 2014;55(42):5846–50.

[8] Yamaguchi K, Noda T, Higuchi Y, Aoki N, Yamaguchi R, Kubo M, et al. Solid-phase synthesis of benzazoles, quinazolines, and quinazolinones using an alkoxyamine linker. Tetrahedron Lett 2014;55(42):5793–7.

[9] Cheng J, Qin J, Guo S, Qiu H, Zhong Y. Design, synthesis and evaluation of novel HDAC inhibitors as potential antitumor agents. Bioorg Med Chem Lett 2014;24(19):4768–72.

[10] Madabhushi S, Mallu KKR, Vangipuram VS, Kurva S, Poornachandra Y, Kumar CG. Synthesis of novel benzimidazole functionalized chiral thioureas and evaluation of their antibacterial and anticancer activities. Bioorg Med Chem Lett 2014;24(20):4822–5.

[11] Turtaut F, Lopez M, Ouahrani-Bettache S, Köhler S, Winum J-Y. Oxo- and thiooxo-imidazo[1,5-c]pyrimidine molecule library: Beyond their interest in inhibition of *Brucella suishistidinol* dehydrogenase, a powerful protection tool in the synthesis of histidine analogues. Bioorg Med Chem Lett 2014;24(21):5008–10.

[12] Nagarajan S, Shanmugavelan P, Sathishkumar M, Selvi R, Ponnuswamy A, Harikrishnan H, et al. An eco-friendly and water mediated product selective synthesis of 2-aminopyrimidines and their in vitro anti-bacterial evaluation. Bioorg Med Chem Lett 2014;24(21):4999–5007.

[13] Hirsch DR, Cox G, D'Erasmo MP, Shakya T, Meck C, Mohd N, et al. Inhibition of the ANT(2″)-Ia resistance enzyme and rescue of aminoglycoside antibiotic activity by synthetic α-hydroxytropolones. Bioorg Med Chem Lett 2014;24(21):4943–7.

[14] Wen W, Wu W, Weaver CD, Lindsley CW. Discovery of potent and selective GIRK1/2 modulators via 'molecular switches' within a series of 1-(3-cyclopropyl-1-phenyl-1H-pyrazol-5-yl)ureas. Bioorg Med Chem Lett 2014;24(21):5102–6.

[15] Venkatraj M, Ariën KK, Heeres J, Joossens J, Dirié B, Lyssens S, et al. From human immunodeficiency virus non-nucleoside reverse transcriptase inhibitors to potent and selective antitrypanosomal compounds. Bioorg Med Chem 2014;22(19):5241–8.

[16] El-Dahshan A, Al-Gharabli SI, Radetzki S, Al-Tel TH, Kumar P, Rademann J. Flexible, polymer-supported synthesis of sphingosine derivatives provides ceramides with enhanced biological activity. Bioorg Med Chem 2014;22(19):5506–12.

[17] Wammes AEM, Hendriks TG, Amatdjais-Groenen HIV, Wijdeven MA, van Hest JCM, van Delft FL, et al. Influence of azide incorporation on binding affinity by small papain inhibitors. Bioorg Med Chem 2014;22(20):5593–603.

Further reading

Papers on combinatorial chemistry or solid-phase synthesis from other journals

Brackett CM, Melander RJ, An IH, Krishnamurthy A, Thompson RJ, Cavanagh J, et al. Small-molecule suppression of β-lactam resistance in multidrug-resistant gram-negative pathogens. J Med Chem 2014;57(17):7450–8.

Feast GC, Lepitre T, Mulet X, Conn CE, Hutt OE, Savage GP, et al. The search for new amphiphiles: synthesis of a modular, high-throughput library. Beilstein J Org Chem 2014;10:1578–88.

Fuse S, Matsumura K, Wakamiya A, Masui H, Tanaka H, Yoshikawa S, et al. Elucidation of the structure–property relationship of p-type organic semiconductors through rapid library construction via a one-pot. Suzuki–Miyaura coupling reaction. ACS Comb Sci 2014;16(9):494–9.

Gad WA, Al-Harbi HD. Microwave-assisted synthesis of pyrido[4,3-d]pyrimidine derivatives and their biological evaluation. Org Chem Indian J 2014;10(12):484–93.

Han M, Song C, Hahn H-G, Jeong N. Exploration of 3-aminoazetidines as triple reuptake inhibitors by bioisosteric modification of 3-α-oxyazetidine. ACS Med Chem Lett 2014;5(9):999–1004.

Jbara M, Seenaiah M, Brik A. Solid phase chemical ligation employing a Rink amide linker for the synthesis of histone H2B protein. Chem Commun (Cambridge, UK) 2014;50(83):12534–7.

Karageorgis G, Warriner S, Nelson A. Efficient discovery of bioactive scaolds by activity-directed synthesis. Nat Chem 2014;6(10):872–6.

Kowalczyk R, Brimble MA, Tomabechi Y, Fairbanks AJ, Fletcher M, Hay DL. Convergent chemoenzymatic synthesis of a library of glycosylated analogues of pramlintide: structure–activity relationships for amylin receptor agonism. Org Biomol Chem 2014;12(41):8142–51.

Kulchat S, Meguellati K, Lehn J-M. Organocatalyzed and uncatalyzed C[n.63742]C/C[n.63742]C and C[n.63742]C/C[n.63742]N exchange processes between Knoevenagel and imine compounds in dynamic covalent chemistry. Helv Chim Acta 2014;97(9):1219–36.

Lemrova B, Smyslova P, Popa I, Ozdian T, Zajdel P, Soural M. Directed solid-phase synthesis of trisubstituted imidazo[4,5-c]pyridines and imidazo[4,5-b]pyridines. ACS Comb Sci 2014;16(10):558–65.

Mali SM, Ganesh Kumar M, Katariya MM, Gopi HN. HBTU mediated 1-hydroxybenzotriazole (HOBt) conjugate addition: synthesis and stereochemical analysis of β-benzotriazole N-oxide substituted γ-amino acids and hybrid peptides. Org Biomol Chem 2014;12(42):8462–72.

Mendez Y, Perez-Labrada K, Gonzalez-Bacerio J, Valdes G, de los Chávez MA, Osuna J, et al. Combinatorial multicomponent access to natural-products-inspired peptidomimetics: discovery of selective inhibitors of microbial metallo-aminopeptidases. ChemMedChem 2014;9(10):2351–9.

Peshkov VA, Peshkov AA, Pereshivko OP, Van Hecke K, Zamigaylo LL, Van der Eycken EV, et al. Three-component reaction of a 2-aminoazine, a 2-oxoaldehyde, and a cyclic 1,3-dicarbonyl compound for the synthesis of imidazo[1,2-a]azine derivatives. ACS Comb Sci 2014;16(10):535–42.

Ponader D, Igde S, Wehle M, Maerker K, Santer M, Bleger D, et al. Photo-switchable precision glycooligomers and their lectin binding. Beilstein J Org Chem 2014;10:1603–12.

Sivanathan S, Scherkenbeck J. Cyclodepsipeptides: a rich source of biologically active compounds for drug research. Molecules 2014;19(8):12368–420.

Tabor RF, Tan DD, Han SS, Young SA, Seeger ZLE, Pottage MJ, et al. Reversible pH- and photocontrollable carbohydrate-based surfactants. Chem Eur J 2014;20(43):13881–4.

Taipa MA. Immunological assays: biotools for high throughput screening and characterisation of combinatorial libraries. Adv Comb Chem High Throughput Screening 2014;1:130–58.

Wang J, Kaiser M, Copp BR. Investigation of indolglyoxamide and indolacetamide analogues of polyamines as antimalarial and antitrypanosomal agents. Mar Drugs 2014;12(6):3138–60.